Laboratory Safety Second Edition

PRINCIPLES AND PRACTICES

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Human Immunodeficiency Virus Type 1 and Other Blood-Borne Pathogens

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INTRODUCTION

Laboratory-acquired infections from blood-borne pathogens have been recognized since 1949 when a laboratory worker was reported to have been infected with "serum hepatitis" in a blood bank (161). Skinhoj (242, 243) reported subsequent increases in occurrences in laboratory-acquired hepatitis and found a sevenfold higher rate of hepatitis in laboratory workers when compared with the general population.

The potential occult infectivity of blood has been emphasized since the documentation of occupationally transmitted human immunodeficiency virus (HIV) infection. As of October 1993, 39 documented occupationally acquired infections with HIV-1 have been reported, with an additional 81 possible work-related infections (134). Since the first occupational transmission was reported in 1984 (4), health care and laboratory administrators, as well as those in the public sector, have re-examined the infection control aspects of their work practices and have begun to develop equipment and procedures to minimize exposures. Because infection with HIV is not always clinically apparent and the infectious potential of blood and other body fluids is not always known, the Centers for Disease Control (CDC) recommended "universal blood and body fluid precautions" in 1987 (42). This approach emphasizes the consistent use of blood and body fluid precautions for *all* patients and their clinical specimens and tissues.

The "universal precautions" strategy has formed the foundation for federal guidelines through the CDC and regulations from the Occupational Safety and Health Administration (OSHA) (see OSHA standard, Appendix II). Both organizations recognize that this practical approach to safety will not only minimize the risk of occupationally acquired HIV-1 infection but will also serve to protect against occupational infection with other blood-borne pathogens such as hepatitis B, hepatitis C, human T-cell leukemia viruses I and II, or HIV-2.

This chapter provides an overview of the epidemiology, risk of transmission, and the recommended or regulated strategies to prevent occupational transmission of HIV and other blood-borne pathogens (the hepatitis viruses were discussed in detail in Chapter 3). All laboratory workers are encouraged to keep abreast of applicable rules or recommendations from federal, state, or professional agencies.

HUMAN IMMUNODEFICIENCY VIRUS TYPE 1

On June 5, 1981, the CDC reported several cases of *Pneumocystis carinii* pneumonia in young male

homosexuals (31). Several weeks later, Kaposi's sarcoma was reported in 26 male homosexuals, some of whom also were diagnosed with *P. carinii* pneumonia (32). These reports represented the first recognized cases of what is now defined as AIDS. Twelve years later, in September 1993, more than 339,000 AIDS cases had been reported to the CDC among persons of all ages in the United States (61), with an estimated 8 to 10 million infected adults and 1 million infected children throughout the world (57).

Within 3 years of the recognized syndrome, the virus causing AIDS was isolated and found to be a new human retrovirus (12, 96, 212). Retroviruses had been studied primarily in animal diseases but were found to be a cause of a human disease in 1980 by Poiesz et al. (209). Although the virus that causes AIDS was originally called human T-cell lymphotropic retrovirus III (HTLV-III) by Gallo and lymphadenopathy-associated virus by Montagnier, the virus has subsequently been termed *HIV-1* by committee (67).

Biological Characteristics

Certain biological characteristics of HIV-1 are important to the epidemiologic and clinical aspects of the disease and contribute to the risk involved with viral transmission. These include (16)

1. HIV-1 belongs to a group of RNA viruses known as human retroviruses, named for the novel reverse transcriptase (RT) enzyme. The RT enzyme allows a DNA chain to be copied from the viral RNA. The double-stranded DNA material from the viral template is then incorporated into the host cell genome. This step is important epidemiologically because the retroviruses are able to exist in a latent phase for prolonged periods before disease develops. More specifically, HIV-1 belongs to the lentivirus group (lenti- = "slow"). It is estimated that the average incubation period between HIV-1 infection and the development of the disease AIDS for both homosexual men and adults with transfusion-associated HIV infection via transfusion is 8 years (171). For infants infected with HIV via transfusion, the estimated incubation period is approximately 2 years (172).

2. The RT enzyme is a natural target for antiviral agents. For example, zidovudine (AZT) inhibits HIV-1 replication by blocking RT activity.

3. Because RT activity is specific for replication of retroviruses, its detection provides an excellent indicator of retroviral activity in laboratory tests.

4. The polymerase enzyme of HIV that is involved in transcription is error-prone, contributing to the antigenic hypervariability on the viral envelope. This complicates the development of a universal vaccine and perhaps influences the virulence of the different strains of virus.

5. Surrounding the RNA viral core and viral enzymes, the lipoprotein envelope contains several important glycoproteins that help bind the virus to host cell receptors and are the focus of several vaccine studies. Evidence of antibodies to glycoproteins GP120, GP160, and GP41 is essential to laboratory testing for infection with HIV-1 (268).

6. Retroviruses, like other enveloped viruses, are rapidly destroyed by common laboratory disinfectants and detergents (151).

7. The HIV-1 viruses replicate intracellularly in the host. The main target cells are those that possess the CD4 protein receptor, primarily the T4 lymphocytes. The T4 cell is lysed or severely limited in function by viral replication, leading to eventual depletion of immunologic capabilities.

The monocyte-macrophage cell, another target cell for HIV-1, harbors the virus but is more resistant to the cytopathic effects. The monocyte-macrophage cell serves as a reservoir for the latent viral state, a "Trojan horse" that transports the virus throughout the body, protecting it from host defenses. Evidence also indicates the Langerhans cells of the skin may also harbor the virus (21).

8. The HIV-1 virus is found in body fluids as cell-associated as well as cell-free. The numbers of virally infected cells and infectious viruses in plasma vary with the stage of HIV-1 infection. For example, HIV p24 antigen, a marker of HIV-1 replication, has been demonstrated during the acute stage of HIV infection and at the late stages of infection when CD4 lymphocytes decrease in number (232). Also, increased HIV-1 plasma titers are associated with the later stages of the disease (130). This higher "dose" of virus may be an important determinant of an increased risk of viral transmission.

9. The HIV-1 virus has been cultured from blood (96), semen (274), vaginal and cervical secretions (210, 264), saliva (112), breast milk (258), tears (93), urine (165), cerebrospinal fluid (131), alveolar fluid (275), and amniotic fluid (194); however, proven human transmission of the virus has only occurred via blood, bloody body fluids, semen, vaginal-cervical secretions, breast milk, or concentrated viral material.

Inactivation Studies

Retroviruses are classified by Klein and Deforest (151) as protein and lipid viruses and, as such, are susceptible to many common disinfectants found in the laboratory. Since 1984, several studies have eval-

TABLE 1 Environmental survival of HIV-1

Condition	Temp. (°C)	Parameters	D_{10}[a]	Comments	References
Heat	60	2 min		Virus in factor VIII preparations	McDougal et al. (185)
	60	2 h		ophilized virus	McDougal et al. (185)
	56	10 min			Martin et al. (177)
	56	20 min		50% serum	Spire et al. (246)
	56	10 min	2 min		McDougal et al. (185)
	56	5 h	20 min	50% plasma	Resnick et al. (224)
	50		24 min		McDougal et al. (185)
	45		3.3 h		McDougal et al. (185)
	37		4.8 days		McDougal et al. (185)
	37	11 days		50% plasma	Resnick et al. (224)
	37	6 days		Dried virus	Prince et al. (216)
Aqueous solution	RT[b]	15 days			Resnick et al. (224)
	RT	>7 days			Barre-Sinoussi et al. (13)
Dried virus	RT	>3 days	9 h	50% plasma in petri dish	Resnick et al. (224)
	RT	>7 days			Barre-Sinoussi et al. (13)
	RT	>7 days	8 h	5% serum on glass	Prince et al. (216)

[a]D_{10}, amount of time required to reduce viral infectivity by 1 log or 90%.
[b]RT, room temperature (20 to 27°C).

uated the inactivation of HIV-1 by a variety of physical and chemical means. The methods of testing for viability of HIV-1 after exposure to disinfectants or physical methods include the determination of RT activity and the ability of the treated virus to infect T-cell lines in tissue culture. The tissue culture assay appears to be more sensitive for small amounts of virus than the RT assay (224). It is yet unknown if the tissue culture assay is able to measure the critical human infectious dose. Therefore, the observed log reductions in virus titer and extrapolated decay rates using high concentrations of virus allow for inferences about effectiveness of the disinfectant or method of inactivation.

Environmental Stability

Under experimental laboratory conditions and grown in high concentrations of 7 to 10 logs tissue culture infectious dose ($TCID_{50}$), HIV-1 demonstrates stability at room temperature both in the dry or liquid form. (One $TCID_{50}$ is the amount of virus required to infect half the cells in tissue culture.) In aqueous suspensions of tissue culture fluid, the virus has remained viable after 1 to 2 weeks (224). Several authors have demonstrated the recovery of viable HIV-1 after 3 to 7 days in the dried state as a viral film on glass or a petri dish (13, 216, 224). Resnick et al. (224) and Prince et al. (216) calculated the amount of time required to reduce viral infectivity by 1 log or 90% (the D_{10} value) in a dried state at room temperature to be 8 to 9 h. It follows that a blood spill containing 1 to 3 logs of virus per milliliter (130) in a clinical or laboratory setting could potentially contain viable HIV-1 for more than 1 day if allowed to dry. Prompt cleaning with appropriate disinfectants should be initiated to remedy this situation.

Heat Inactivation

Although HIV-1 appears stable at room temperature, it is very heat-labile. McDougal et al. (185) found that the virus follows first-order kinetics and calculated the D_{10} values for a series of temperatures (Table 1). In a liquid suspension, they found little difference in the thermal decay rate when the virus was suspended in culture medium, serum, or liquid factor VIII but found that the virus in the lyophilized state was somewhat resistant to heat.

Martin, as well as other authors (177, 246), reported inactivation of HIV-1 suspensions at 56°C within 10 to 20 min (D_{10} value = 2 min). Resnick et al. (224), however, found that heating at 56°C for 5 h was necessary, calculating a D_{10} value of 20 min. The reason for discrepancies in these studies is undetermined.

A 1988 survey of laboratories evaluating HIV-1 tests for the CDC (52) reported that 3.9% of the laboratories heat-inactivated serum specimens at 56°C as a safety measure before testing. However, the heating process can cause false-positive results for enzyme immunoassay and Western blot tests (108, 180), changes in laboratory enzyme levels, and turbidity problems with plasma (156). The CDC recommended that heat inactivation of serum does not preclude the use of standard precautions and should *not* be used as a routine means of protection of laboratory workers (52).

The heating process has better applicability in the preparation of safe therapeutic blood products. Piszkiewicz et al. (207) found that pasteurization of antithrombin III concentrate at 60°C for 7 min reduced HIV-1 to below detectable levels. Others have found alternative methods of inactivation of blood products, including exposure to tri-(*n*-butyl)-phosphate and sodium cholate for 20 min at room temperature (214). A promising method that destroys HIV-1 but does not effect changes in hematologic parameters is the "photodynamic method," a hematoporphyrin photosensitizer (179).

Physical Methods of Inactivation

Spire et al. (246) demonstrated that HIV-1 is fairly radio-resistant, requiring higher doses of both gamma and UV irradiation for inactivation of the virus than the doses routinely used for food irradiation or in laminar flow safety cabinets. Martin et al. (176) found that sonication does not destroy HIV-1, but both high pH and low pH (<1 or >13) will inactivate the virus. Kempf et al. (148) also found that the virus is inactivated at a pH less than 4 when suspended in immunoglobulin.

Chemical Inactivation

Although the virus survives in liquid cultures for more than 2 weeks (224) and in the dried state for more than 3 days (13, 216, 224), results have confirmed that, in most cases, disinfectants at concentrations below commonly used levels are sufficient to inactivate high titers of HIV-1. Table 2 lists several chemical disinfectants and the parameters tested. Most conditions of testing in these studies have represented in-use situations such as room temperature (21 to 25°C) or less than 10-min exposure times.

Resnick et al. (224) found that common chemicals frequently used in laboratory procedures inactivated the virus. For example, nonionic detergent (Nonidet P-40) inactivated HIV-1 at 0.5% and is used in the preparation of disrupted virus at a concentration of 1%. The laboratory fixative, acetone:alcohol, also was found effective against HIV-1 after 20 min of exposure. Martin et al. (176, 177) tested paraformaldehyde (used as a laboratory fixative at 1%) and found that infected cells treated with >0.1% paraformaldehyde could no longer transmit the virus to susceptible cells.

Disinfectants that are effective against aqueous HIV-1 suspensions cannot be assumed to be equally effective against dried HIV-1. Data exist that show other viruses are more resistant to disinfectants in a dried state than suspended viruses (151, 167, 237). Several studies found alcohols to be effective against HIV-1 in culture suspensions (177, 224, 247); however, Hanson et al. (116) failed to inactivate dried, cell-free HIV within 10 min of exposure to 70% ethanol. The use of 70% ethanol as a laboratory surface disinfectant should be carefully reconsidered.

The standard antiseptics povidine-iodine and chlorhexidine gluconate, as well as common disinfectants used in the clinical setting (bleach, quaternary ammonium chlorides, phenolics, and glutaraldehyde), quickly inactivate the virus in culture (see Table 2). Hanson et al. (116) found 1% glutaraldehyde effective against dried HIV-1 at 1-min exposure but found it failed to inactivate the dried virus even after 15 min when serum was added. Other data have also shown that lipophilic viruses, including HIV, become appreciably resistant (or the disinfectant less active) in the presence of high organic load such as in blood, semen, and feces (216). Increasing the concentration of disinfectant, increasing exposure time, or simply removing as much of the organic load as possible by thorough cleaning before disinfection is recommended to alleviate this problem (see also Chapter 3).

Discrepancies in the studies to date may be explained by the variety of methodologies used to determine virucidal activity such as testing culture suspensions versus dried virus on carriers, end point determinations, organic load, contact times, neutralizers, and composition of cell culture media. Perhaps variation in HIV-1 strains may also account for differences in resistance to germicides. The need for an internationally accepted standard for virucidal assays was expressed by the American Society for Microbiology Working Group for Viruses at a symposium evaluating chemical germicides (215). Because most of the studies on inactivation of HIV-1 have tested suspension cultures of extracellular HIV-1, the Working Group called for additional data on dried viruses with an organic load challenge.

The Environmental Protection Agency has developed guidelines for the testing of virucides that involve the use of dried viral films on carriers such as glass slides or petri dishes (83) and are the basis for virucide registration in the United States. Recently,

TABLE 2 Chemical and physical methods of inactivating HIV[a]

Method	Concentration tested with RTA[b] reduction	Concentration tested reducing >10^5 TCID[c] HIV	Comments	References
Chemical				
Disinfectants				
Sodium hypochlorite	—[d]	0.1%		Martin et al. (177)
	—	0.5%		Resnick et al. (224)
	0.2%	—		Spire et al. (235)
Chlorine dioxide (LD)	1:200	1:200		Sarin et al. (235)
Alcohol	—	70%		Resnick et al. (224)
Ethanol	25%	—		Spire et al. (247)
	—	50%		Martin et al. (177)
	—	70%	Dried, cell-free virus >10 min required	Hanson (116)
Isopropyl	—	35%		Martin et al. (177)
Methylalcohol: acetone	—	1:1	20 min required	Resnick et al. (224)
Quaternary ammonium chloride	—	0.08%		Resnick et al. (224)
Hydrogen peroxide	—	0.3%		Martin et al. (177)
Phenolic	—	0.5%		Martin et al. (177)
Paraformaldehyde	—	0.5%		Martin et al. (177)
	—	0.1%	2 h	Martin et al. (176)
Neutral buffered formalin	—	1%		Martin et al. (176)
Nonidet P-40	—	0.5%	In 50% human plasma	Resnick et al. (224)
	—	1.0%		Martin et al. (177)
Glutaraldehyde	1%	—		Spire et al. (247)
	—	1%	Dried, cell-free	Hanson et al. (116)
	—	2%	Dried, in serum	Hanson et al. (116)
	—	1%	Dried, in serum Requires >15 min	Hanson et al. (116)
	—	2%	Dried, cell-associated	Hanson et al. (116)
Sodium hydroxide	40 mmol/liter	—		Spire et al. (247)
Antiseptics				
Povidone-iodine	—	0.25%	37°C	Kaplan et al. (145)
	—	0.5%	37°C	Harbison and Hammer (118)
Chlorhexidine gluconate	—	0.2% (1:20)	37°C	Harbison and Hammer (118)
Physical				
Gamma irradiation	2.5×10^5 rad			Spire et al. (246)
UV radiation	5×10^3 J/m^2			Spire et al. (246)
pH	—	<1, >13		Martin et al. (177)
	—	<4	Virus in IgG	Kempf et al. (148)

[a]All tests conducted at room temperature and <10 min contact time unless otherwise noted.

[b]RTA, reverse transcriptase activity.

[c]TCID, tissue culture infectious dose.

[d]Not tested by the given method.

the Environmental Protection Agency TSS-7 guidelines have been used for approved testing protocols for HIV inactivation (215). In general, HIV-1 is inactivated by chemical germicides that are effective against lipophilic viruses. Labels of Environmental Protection Agency-registered disinfectants should be scrutinized for virucidal claims and directions for in-use concentrations should be followed.

The HIV-1 virus has not been shown to be transmitted to date through environmental exposures, although the potential exists for inadvertent contamination of hands by touching soiled surfaces and subsequent inoculation of mucous membranes. The risk for this mode of exposure increases in a research laboratory situation in which high titers of virus may be manipulated. Routine cleaning and prompt decontamination of spills are the best methods to minimize this risk. In fact, the CDC does not recommend any changes in the standard guidelines for sterilization, disinfection, or housekeeping practices to handle HIV-1 (42).

Epidemiology

Since the recognition and reporting of AIDS in 1981, more than 339,000 persons with AIDS have been reported to public health departments in the United States for a nationwide rate of 17.2 per 100,000 (61). More than 204,000 (60%) of these have died. In 1992, AIDS became the leading cause of death among U.S. men 25 to 44 years of age and the fourth leading cause of death among U.S. women 15 to 44 years of age (60).

Epidemiologic information gathered since the early 1980s indicates that the modes of transmission of HIV-1 have remained the same. HIV-1 is transmitted through sexual contact, percutaneous or mucous membrane exposure to blood, birth or breast feeding from an infected mother, or transfusion of HIV-contaminated blood. Homosexual-bisexual men and intravenous (IV) drug users have represented more than three-fourths of all AIDS cases reported from 1981 to 1990 (56). However, the largest recent proportionate increases have occurred among women, blacks, Hispanics, persons living in the South, and persons exposed through heterosexual contact. Cases in children associated with perinatal HIV transmission have also continued to rise.

The annual incidence of AIDS cases associated with blood transfusions and therapeutics for hemophilia has stabilized since the serologic screening of blood donations and heat treatment of clotting factors was initiated in 1985. Currently, it is estimated that the risk of any unit of blood being contaminated with HIV after the screening process is 1:150,000 (69). Immune globulin preparations (40), recent therapeutic products for hemophilia patients (49), and hepatitis B vaccines prepared from pooled human sera (35) have been shown to be free of the virus.

In 1993, 4.7% of all AIDS cases were assigned to a "no identified risk" (NIR) category, representing a large caseload of those recently diagnosed (61). For many of these cases, follow-up investigation is incomplete or the patient died before an investigation could be performed. Historically, on investigation, 83% of the NIRs are classified into an identified risk category. Overall, the NIR category represents about 3% of all reported AIDS cases. Generally, 10% of the NIR cases are health care workers, and this percentage has remained stable over time (57).

Occupational HIV-1 Transmission

AIDS in Health Care Workers

National surveillance data of health care workers demonstrate that there is no higher risk for developing AIDS in those working in the health care or laboratory setting than for those in the general public. As of 1988, approximately 5.3% of reported AIDS cases with a known work history had related a history of working in a health care or laboratory setting since 1978 (63). This percentage is comparable to the proportion of the U.S. population working in health care (5.7%) (25). Moreover, 95% of this group have recognized nonoccupational risk factors. Health care workers with AIDS are more likely to be homosexual or bisexual than other persons with AIDS. After surveillance investigations are completed, only 1.4% of health care workers with AIDS are classified with NIR other than employment in a health care setting (63). Further examination of the remaining NIR cases in health care workers shows that they are demographically more similar to other AIDS cases than to health care workers in general. For example, 73% of the NIR health care workers versus 23% of all U.S. health care workers are male (25). Also, the only occupation that is overrepresented among the NIR cases is that of maintenance workers (20% for NIR cases versus 6% for cases with identified risk, $P<0.004$) (63) and not the occupations that are at risk for percutaneous blood exposures such as surgeons or laboratory technologists.

More indirect evidence that the risk of transmission of HIV-1 in the health care setting is small is found in 13 HIV prevalence studies conducted on cohorts of health care workers around the country, many of whom work in areas of high community seroprevalence (18, 79, 100, 106, 119, 129, 153, 170,

175, 239, 267–269). These prevalence studies have examined 6,619 U.S. health care workers with 1,208 reported HIV exposures and found 8 seropositive (0.12%) health care workers with no identified community risk. The prevalence of infection in health care workers does not appear to be any higher than that of the comparable population-at-large.

The lack of association of HIV transmission in the health care setting has also been demonstrated in prevalence studies from Kinshasa, Zaire (173, 199), where community prevalence of HIV is high (8.4% in women attending an antenatal clinic and 6.5% among men donating blood). No higher rates of seropositivity were found in the hospital staff, nor were there any significant differences among the medical, administrative, and manual workers (6.5, 6.4, and 6%, respectively). Of note is a lack of seroconversion in laboratory workers between 1984 and 1986 (199). This finding is important when differences in infection control practices in the developing countries are compared with those in the United States and Europe. For example, resources such as gowns, gloves, and disinfectants are not routinely available, and needles and syringes are nearly always washed by hand, then sterilized for reuse. These findings reaffirm the apparent low risk for occupational transmission of HIV.

Documented Case Studies

Occupational HIV infection after a specific exposure is the best indicator of the mode of HIV transmission in the health care setting. Although the risk of occupational HIV transmission appears to be low, a few case reports of health care workers infected with the virus through occupational exposure have been reported. Since 1981, 39 health care workers have experienced clearly defined seroconversions after exposures (4, 5, 39, 42, 43, 46, 47, 101, 107, 114, 123, 134, 136, 168, 169, 188, 198, 202, 218, 254, 256, 260, 265, 267). The modes of transmission for these infections appear to be 34 (87%) percutaneous (i.e., needlestick, laceration, blood in nonintact skin), 4 (10%) mucocutaneous, and 1 (3%) both percutaneous and mucocutaneous. Thirty-six (92%) of the exposures that resulted in infection were to blood; one exposure was to visibly bloody fluid, one to an unspecified fluid, and one to concentrated virus in the laboratory. Also, 81 possible occupational transmissions have been reported from health care workers who have been investigated and are without identifiable behavioral or transfusion risks but who have experienced nondocumented percutaneous or mucocutaneous exposures or contact with laboratory levels of HIV (6, 9, 14, 27, 28, 106, 111, 115, 134, 153, 166, 211, 236, 267, 269).

Sixteen laboratory workers per se have documented seroconversions, representing the largest health care occupation group among the 39 infected workers (41%) (134). Examples of specific exposures that resulted in infections include cuts with contaminated objects such as a broken Vacutainer tube (123) or a blunt stainless steel cannula used to clean equipment contaminated with concentrated virus (267). Before "universal precautions" were recommended in 1987, a laboratory worker's bare hands and arms were contaminated from a blood spill from an apheresis machine. The worker also had dermatitis and, subsequently, seroconverted (43). Fifteen additional laboratory workers are among those with possible occupational infections with no documented specific exposure that resulted in seroconversion (134).

Occupational Risk Assessment

Prevalence and epidemiologic studies indicate that occupational HIV infection does not occur frequently. Documented HIV seroconversions caused by exposures demonstrate that an occupational risk of HIV transmission does exist. Factors that may contribute to the magnitude of that risk have been addressed by Henderson (121) and include the type or extent of injury, the body fluid involved, the "dose" of inoculum, environmental factors, and recipient susceptibility. The interactions and additive effect of these factors on the individual laboratory worker are complex and unknown. However, some data are available that can help further define risks associated with several procedures or circumstances.

Route or Extent of Exposure

Parenteral. Of the 39 occupationally acquired HIV infections reported, 34 (87%) have been associated with parenteral exposure (needlesticks, cut with contaminated objects, or nonintact skin exposure to blood). Many of these have been associated with an extensive injury (4, 42, 47, 122, 182, 254, 267) involving partial injection of blood or deep intramuscular injections or cuts. However, at least three have described only superficial injuries (28, 198, 202).

The best direct measure of risk of HIV transmission by a single exposure is accomplished through prospective cohort studies that document an HIV exposure event with follow-up serologic monitoring of the exposed health care worker (Table 3). In 15 prospective studies to date that have reported 3,579 percutaneous exposures in health care workers, 8 instances of seroconversion have been documented, for an overall risk of transmission per

TABLE 3 Summary of published prospective studies of the risk for occupational HIV-1 transmission in the clinical setting

Exposure type (references)	No. of studies	No. of HCWs[a]	No. of exposures	No. infected	Infection rate (%)
Percutaneous (80, 90, 100, 123, 125, 136, 142, 154, 187, 208, 218, 219, 259, 273)	15	3,328	3,579	8	0.25
Mucous membrane (80, 90, 100, 123, 136, 142, 154, 187, 218, 219, 259, 273)	13	906	1,364	1	0.07
Cutaneous (123)	1	149	5,568	0	0
Routine patient care activities (no exposures) (100, 122, 154)	3	929	NA[b]	0	0

[a]HCWs, health care workers.

[b]NA, not applicable.

percutaneous injury from an HIV-infected source of 0.25% (80, 90, 100, 123, 125, 136, 142, 154, 187, 208, 218, 219, 259, 273).

Mucous membrane. Four mucous membrane exposures resulting in HIV infection have been reported in health care workers (43, 107, 134), although in one instance, nonintact skin contact with blood could not be ruled out as a route of exposure. In this case, a laboratory worker's face was splattered with blood when a Vacutainer top flew off the tube while collecting blood from a patient. She also reported having acne (43).

Thirteen prospective studies have included mucous membrane exposures in their risk evaluations and have reported only one seroconversion from 1,364 exposures (80, 90, 100, 123, 136, 142, 154, 187, 218, 219, 259, 273). Therefore, the risk of transmission of HIV via mucous membrane exposure is extremely low (0.07%), much lower than that of a percutaneous injury (i.e., <0.3% per exposure).

Cutaneous. The identification of the Langerhans cell in the subepithelial tissue as a target cell for the HIV (21) has caused concern among some health care workers that cutaneous exposure to HIV may result in transmission of the virus via these cells into the body (73). Infection of the Langerhans cells is usually a consequence of septic HIV infection (21). Enormous protection against all pathogens is provided by intact skin; however, penetration of the skin into the subepithelial tissues and subsequent inoculation of the Langerhans cells might occur during a needlestick or cut injury or other breaks in the skin (99).

One reported case of HIV transmission via skin contact has been reported in a mother caring for her HIV-infected child (39). Although no specific cuts, punctures, or splashes were noted, the mother reported that she used no barrier precautions such as gloves or gowns and did not always wash her hands after caring for her child. She frequently handled blood and bloody body fluids. It is likely that tiny cuts on the skin may have actually been the route of transmission of the virus.

A report of a laboratory worker infected with a laboratory strain of HIV (267) considered the source of that exposure to be "contact of the individual's gloved hand with H9/HTLV-III_B culture supernatant with inapparent and undetected exposure to skin." The subject worked with concentrated HIV and reported wearing gowns and gloves routinely. The subject admitted episodes when pinholes or tears in gloves required that they be changed. The subject also related accounts of leakage of virus-positive culture fluid from equipment and the subsequent decontamination efforts with a hand brush. The subject also recalled an episode of nonspecific dermatitis on the arm that was always covered by a gown.

A subgroup of 98 other laboratory workers who also worked with concentrated HIV were seronegative. An incidence rate of 0.48 per 100 person-years exposure has been calculated for prolonged laboratory exposure to *concentrated* virus, approximately the same magnitude of risk of infection as health care workers who experience a needlestick HIV exposure (267). Over a 45-year career, this rate would lead to a risk of 195 infections per 1,000 exposed workers in research and production facilities.

Three prospective studies have reviewed the risk of HIV transmission as a result of routine patient care activities without a known percutaneous or mucous membrane exposure (100, 122, 154). None of the 929 health care workers studied have been infected. Recently, Henderson et al. (123) summarized a 6-year ongoing study of the risk of HIV transmission to health care workers sustaining a variety of occupational exposures, including cutaneous exposure. Responding to a questionnaire, 149 National

Institutes of Health (NIH) workers reported 5,568 cutaneous exposures to blood or other bodily fluids from HIV-infected patients or their specimens and more than 10,000 cutaneous exposures to blood from all patients. No seroconversion occurred from these exposures despite the high frequency of occurrence, confirming the lack of evidence of any measurable risk of transmission of HIV by cutaneous exposure in a clinical setting.

Other routes of exposure. There have been no documented cases of HIV transmission through the respiratory, ingestion, or vector route of exposure. Some have questioned the possibility of respiratory transmission of HIV (139), specifically with the research laboratory-acquired infection with no documented percutaneous exposure (267). It is well known that common laboratory procedures using blenders and centrifuges have been evaluated and shown to produce infectious aerosols (3, 147, 205, 222, 249, 250). Before the CDC and NIH recommendations for biological containment in laboratories, agents such as rabies (271) or arboviruses (117) that are not transmitted by aerosols in the community or clinical setting were documented to cause infection under laboratory conditions when *concentrated* agents were aerosolized by blending or purification procedures. The reported laboratory worker infected with the laboratory strain of HIV may have been exposed to aerosols released during reported rotor-seal failures involving the continuous-flow zonal centrifuge.

However, an expert safety review team convened by the director of the NIH addressed this issue and agreed that the potential for direct contact transmission was much greater than for aerosol transmission (46). Procedures that generated aerosols were carried out in biological safety cabinets (BSCs). They cite other instances involving overt aerosol exposure in laboratory and production facilities involving concentrated HIV that have not resulted in seroconversions in exposed workers (41). Nevertheless, the occurrence of infection through an unknown exposure emphasizes the need for laboratory workers, particularly in research or production facilities, to adhere strictly to published safety guidelines.

The potential for respiratory transmission of HIV in individuals performing aerosol-producing procedures in a clinical setting (i.e., surgery, dentistry) has also been raised (73, 139). No epidemiologic information supports this theory. In fact, several studies have shown a low prevalence of HIV infection in dentists who are routinely exposed to aerosolized body fluids (88, 104, 119, 153, 170). Likewise, surgeons are not overrepresented in the reported AIDS cases compared with other health care workers (63).

Johnson and Robinson (139) demonstrated that HIV can remain viable in cool vapors and aerosols generated by common surgical power instruments but not in the heated vapors produced from electrocautery. In a companion study, Heinsohn et al. (120) demonstrated that aerosols of sub- and micron particle sizes are produced by the instruments. Questions remain whether any respirable size particles generated contain viable HIV and whether there exists an infectious dose required for aerosol transmission of HIV.

Other Factors

Viral concentration. The transmission of HIV and subsequent infection may also depend on the "dose" of the virus present at time of exposure. The dose is determined by the size of the inoculum or the concentration of virus in the inoculum. The dose of HIV required to infect humans is unknown. Fultz et al. (95) studied the infection of chimpanzees with HIV-1 and found that those receiving >1 $TCID_{50}$ by IV injection were persistently infected for up to 18 months. Chimpanzees inoculated with low doses (0.1 $TCID_{50}$) did not become infected, suggesting that immune systems can manage to contain small inocula of virus.

A large inoculum of HIV-infected blood such as a unit of transfused blood carries a higher likelihood of virus transmission. Donegan et al. (76) examined recipients of infected blood units with no other risk factors for HIV infection and found that 89.5% were seropositive. Ho et al. (130) estimated that 250 ml of HIV-contaminated blood contains 10^4 to 10^6 $TCID_{50}$ of HIV. In contrast, a much lower risk is associated with occupational exposures (0.25%) in which the amount of blood involved is unknown but calculated by Ho to contain 0.06 to 7 $TCID_{50}$ of HIV.

The concentration of virus in blood or bodily fluid is dependent on the stage of the patient's illness and the antiviral treatment of the patient (130, 232). Since 1983, the CDC Cooperative Needlestick Surveillance Project (260) has evaluated 1,103 workers with percutaneous injuries that resulted in four seroconversions, all of whom sustained exposures to blood from source patients with CDC-defined AIDS. Saag et al. (232) evaluated the plasma viremia levels in patients infected with HIV and found none of the asymptomatic adults, 12% of adults with AIDS-related complex, and 93% of AIDS patients had cell-free infectious virus in their plasma. Titers of the virus ranged from 10 to 10^8 TCID/ml of plasma, with a mean of $10^{2.8}$ TCID/ml in patients

with AIDS. Patients with acute HIV infection had viral titers of 10 to 10^3 TCID/ml.

Saag et al. (232) also found that therapy with AZT led to a significant decline in titer. Ho et al. (130) found a 25-fold lower titer mean in AIDS patients treated with AZT versus untreated AIDS patients.

Research or production laboratory workers, by the nature of the work performed, are placed at greater risk because of the high viral concentrations in culture (>10^8 TCID/ml). Published recommended barrier protection and precautions developed by the NIH and the CDC reduce worker exposure to high-risk operations (33, 34, 36, 42, 46).

Specimen age. The length of time the blood has been removed from the source before exposure may also influence the number of infectious viruses present in the inoculum. Although most occupational infections have occurred after exposure to "fresh" blood, HIV has demonstrated stability in the environment in both liquid and dry states (224) and may survive for hours to days at room temperature.

Other. Other factors contributing to the overall risk of HIV transmission may include the virulence of the viral strain (10), postexposure first-aid or prophylactic practices, or health care worker-related factors such as skin integrity, immunologic status (100), or inflammation around the exposure site (numbers of $CD4^+$ cells available) (123).

Relative Risk for Occupational Infection

The anxiety surrounding HIV in the laboratory setting has been partially caused by the historical problem of occupational hepatitis B virus (HBV) infection and its designation as a model for transmission of a blood-borne pathogen. The CDC estimates that 12,000 health care workers will become occupationally infected with HBV each year, resulting in more than 250 deaths (51). In contrast, the total number of occupationally acquired HIV infections in 12 years is estimated to be 120 (39 documented, 81 possible). The risk of HBV infection after a parenteral exposure to hepatitis B surface antigen positive blood (6 to 30%) (36) is much greater than the risk of HIV infection from a similar exposure to HIV-infected blood (0.25%). The difference in rate of transmission and numbers of deaths is probably a result of the lower concentrations of virus in the blood of HIV-infected persons compared with that of HBV-infected persons (57). If the incidence of fatality is estimated for hepatitis B as 1 to 2% and for HIV infection as ultimately 100%, the risk of mortality from parenteral exposure to both viruses is essentially the same (0.06 to 0.3%). Repeated exposures will increase the overall risk to the laboratory worker for occupational infection. The hepatitis B vaccine is available and effective if used and is a preventive measure currently unavailable for HIV.

The risk of transmission associated with occupational exposures to other blood-borne pathogens has yet to be determined. Nevertheless, standard precautions taken to prevent exposures to hepatitis B will prevent occupational transmission of HIV and other blood-borne pathogens. A thorough discussion of hepatitis can be found in Chapter 3.

OTHER BLOOD-BORNE PATHOGENS

Retroviruses

Since 1980, five types of human retrovirus have been isolated: HTLV-I, HTLV-II, HIV-1 (formerly HTLV-III), HIV-2 (formerly HTLV-IV), and HTLV-V. Based on morphologic features and molecular hybridization studies, HTLV-I, -II, and -V are classified as oncornaviruses and are associated primarily with malignancies such as leukemia and lymphoma. HIV-1 and HIV-2 have been classified together as lentiviruses (16) and cause cell lysis and death.

Human T-Lymphotropic Virus Type I

HTLV-I, the first human retrovirus to be isolated (209), has been associated with adult T-cell leukemia-lymphoma and with a chronic neurologic disease called tropical spastic paraparesis (105). Compared with HIV-1, HTLV-I infection is a more chronic, endemic infection, largely confined to populations defined by geography, race, and age. Endemic areas appear to be concentrated in southwestern Japan, Africa, the Caribbean basin, and the southeastern United States (17, 127, 272). Although seroprevalence can be high in the endemic areas of Japan (20% of adults) or the Caribbean (2 to 5% of black adults), HTLV-I seroprevalence is low in the general population in the United States. Blood donations screened by the American Red Cross in 1989 found a seropositive HTLV-I/II rate of 1.4 per 10,000 (54), similar to the rate of HIV-1 (1.72 per 10,000) (57).

HTLV-I, like HIV-1, is transmitted by sexual contact, perinatally, and through contaminated blood. HTLV-I is, however, considerably less infectious than HIV-1, and its transmission is closely cell-associated. For example, HTLV-1 has been transmitted through whole blood, packed cells, and platelets but not through fresh-frozen plasma (201) nor through pooled clotting factor concentrates from seropositive donors in the United States (65). Parenteral exposure to contaminated needles is a documented

risk accounting for high rates of seropositivity (18 to 49%) among drug abusers (158, 159, 228). One seroconversion in a health care worker who unintentionally inoculated himself with blood from an infected patient with adult T-cell leukemia-lymphoma has been reported in Japan (146).

Human T-Lymphotropic Virus Type II

A related virus, HTLV-II, was isolated in 1982 from a patient with a T-cell variant of hairy cell leukemia (143). Other cases of infection associated with hematologic abnormalities have been identified, but the HTLV-II involvement in disease is unknown (251). The epidemiology of HTLV-II is unknown because of the paucity of cases and the lack of a specific screening test for HTLV-II (HTLV-I and -II cross-react in the HTLV-I screen). The virus is presumably transmitted via the same mechanisms as HTLV-I. The main known association of HTLV-II seropositivity is IV drug abuse. In one study, a surprising 52% of the HTLV-I/II seropositive U.S. blood donors analyzed by a specific DNA amplification test were infected with HTLV-II and were more associated with a risk factor of IV drug use than the HTLV-I seropositives (160).

Human Immunodeficiency Virus Type 2

In 1986, a second human retrovirus capable of causing AIDS was isolated from patients of West African origin and was named HTLV-IV (144). The virus, later renamed HIV-2, was very closely related to simian immunodeficiency viruses, suggesting a recent divergence from a common ancestor (223).

HIV-2 is endemic to western Africa where it is the dominant HIV. Although HIV-2 seroprevalence rates are high in this region (8.9% of adults in Guinea-Bissau), the rate of AIDS is low (204), suggesting that the ability to cause disease is less efficient in HIV-2 than in HIV-1. HIV-2 cases have also been reported with more frequency in Europe and Canada, and seven cases have been reported in the United States (53). All U.S. subjects had West African origins. The incidence in nonendemic populations is difficult to estimate at this time until more specific laboratory tests become available for widespread screening. The current enzyme immunoassay laboratory tests will only detect 46 to 96% of HIV-2-positive sera (74). A positive enzyme immunoassay test for HIV-1 with an indeterminate Western blot or clinical AIDS with a weak or negative HIV-1 test should raise the possibility of HIV-2 infection (135).

HIV-2 seems to be transmitted in the same way as HIV-1. To date, no occupational infections have been documented, although there is documentation of parenteral transmission through IV drugs and blood transfusions (77).

Human T-Lymphotropic Virus Type V

HTLV-V is the designation given to an apparently new retrovirus isolated from a cluster of patients in southern Italy with a clinical syndrome resembling mycosis fungoides. This virus is significantly cross-reactive with and genetically related to HTLV-I (16). As with HIV-2 and HTLV-II, there is a lack of epidemiologic data regarding HTLV-V.

Future retrovirologic research will no doubt reveal other retroviral agents responsible for other diseases. For example, RT activity has been detected in the cells of Kawasaki disease and may indicate a retroviral etiologic agent (16).

Other Pathogens

Concern over laboratory-acquired infections has focused on HIV and the hepatitis viruses in recent years. Additional infectious diseases may include a septic phase in which agents are found in blood, many for prolonged lengths of time. Table 4 categorizes some of the documented occupationally or nosocomially transmitted blood-borne agents into three transmission groupings:

1. As with HIV and hepatitis viruses, transmission of the agent and subsequent infection of the health care worker might occur after percutaneous or mucous membrane exposure to infected blood.
2. Some infectious agents have been transmitted nosocomially through blood transfusions and pose a *potential* occupational hazard via blood exposure.
3. Other blood-borne agents also infect tissues, and laboratory-acquired infections have occurred via contact with concentrated infectious material or with experimentally infected animals, blood, or excreta.

No published information is available regarding the risk of occupational transmission of any of these agents (Table 4). Most of the agents are rarely found in the United States and may not pose a significant risk at this time. For example, Chagas' disease is endemic in Latin America, where blood transfusions frequently transmit the trypanosomes. However, Kerndt et al. (150) discovered a 2.4% seropositivity rate in Los Angeles after testing more than 1,000 blood donations.

Syphilis cases in the United States, however, are increasing in number with an incidence of 14.6 cases per 100,000 persons, a rate similar to that of HIV and HBV (261). *Treponema pallidum*, the causative agent of syphilis, is found in highest numbers during the

TABLE 4 Nosocomial transmission of blood-borne pathogens other than HIV or hepatitis viruses

1. Agents known to cause occupational infections in health care workers from percutaneous or mucous membrane exposure to blood
   - HTLV-I (146)
   - *Treponema pallidum* (syphilis) (252)
   - *Plasmodium* (malaria) (15, 20, 29)
   - *Borrelia* (261)
   - *Rickettsia rickettsii* (Rocky Mountain spotted fever) (238)
   - *Mycobacterium leprae* (leprosy) (174)
   - Viral hemorrhagic fever viruses:
     - Lassa (89)
     - Marburg (244)
     - Ebola (126)
     - Crimean-Congo (26)
2. Agents known to cause nosocomial transmission of infection through blood transfusions or tattoos (potential occupational hazards)
   - *Treponema pallidum* (syphilis) (252)
   - *Plasmodium* sp. (malaria) (97, 113)
   - *Babesia microti* (110, 245)
   - *Brucella* (261)
   - Colorado tick fever virus (190)
   - Cytomegalovirus (8)
   - *Trypanosoma brucei gambiense* (African trypanosomiasis) (128)
   - *Trypanosoma cruzi* (Chagas' disease) (24, 150)
   - *Leishmania* sp. (24)
   - *Mycobacterium leprae* (leprosy) (203)
   - Parvovirus B19 (191)
3. Blood-borne agents associated with laboratory-acquired infection via highly concentrated material or infected animals
   - *Plasmodium* sp. (malaria) (137)
   - *Leptospira* sp. (leptospirosis) (206)
   - Arboviruses (117)
   - Colorado tick fever virus (248)
   - Ebola virus (81)
   - *Trypanosoma cruzi* (22, 30, 132)
   - *Leishmania* sp. (92, 234)
   - *Toxoplasma gondii* (85, 220)
   - *Rickettsia ricketsii* (Rocky Mountain spotted fever) (140)
   - Parvovirus B19 (68)
   - *Brucella* (133, 206)
   - *Treponema pallidum* (syphilis) (206)
   - Lassa fever virus (162)
   - *Trypanosoma brucei gambiense* (African trypanosomiasis) (229)
   - *Borrelia* sp. (84)

secondary hematogenous stage but is also found intermittently in blood if syphilis is left untreated. Nosocomial transmission of syphilis has occurred by needlesticks, blood transfusions, and tattooing (252), as well as in laboratory environments (206).

Most of these agents have not been implicated in documented occupational infections with clinical exposures, but the amount of infectious agents present during septic phases of infection indicate the real potential for percutaneous transmission. For example, *Babesia microti* is present in 30 to 85% of peripheral red blood cells during the parasitemia stage of infection (255) and has been transmitted through blood transfusions (110, 245). In acute *Brucella melitensis* infections, 70 to 90% of blood cultures will grow the organism (7, 109). Human parvovirus B19 can demonstrate a high viral titer (10^{10} virions/ml) during a brief viremic stage (8) and has been transmitted through blood transfusions. In fact, Barbara and Contreras (8) estimated that up to 90% of recipients of factor VIII are likely to be seropositive for parvovirus B19, the causative agent of erythema infectiosum, also known as fifth disease.

Amplification of some blood-borne agents in the laboratory environment has resulted in laboratory-acquired infections due to contact with higher doses of agent than is found in clinical situations. In many of the reported laboratory-acquired cases listed in category 3 of Table 4, no specific incident for exposure could be recalled. Rather, the infected employee simply "worked with the agent" (117, 206), implying either aerosolization of high titers of organisms or inadvertent inoculation of mucous membranes or nonintact skin. Most of the agents listed in category 3 of Table 4 caused an occupational infection before the publication of the standard laboratory containment guidelines (225) designed to protect laboratory workers from aerosols, splashes, and other hazardous exposures.

Table 4 is not a hierarchy of risk of transmission nor is it all inclusive for blood-borne agents. The agents listed in the table with potential risk of transmission and the increasing prevalence of recognized and new retroviruses should be a reminder that laboratory safety policies should not focus on the risk of transmission of one or two agents. Emphasis should be placed on the development of standard laboratory practices for handling blood and other potentially infectious materials from all human sources in the clinical setting and the need to comply with published safety guidelines based on potential routes of transmission and procedures performed in the clinical and research laboratory environment.

STRATEGIES FOR INFECTION PREVENTION

Within 1 year of the first recognized cases of the newly defined disease AIDS, the CDC issued guidelines (33) for clinical and laboratory staff regarding appropriate precautions for handling specimens collected from AIDS patients. Updates from the CDC in 1983 (34) and 1985 (37, 38) re-emphasized precautions that had been recommended previously for handling specimens from patients known to be infected with hepatitis B (i.e., minimizing the risk for transmission by the percutaneous, mucous membrane, and cutaneous routes of infection). After anecdotal laboratory-associated infections with HIV were reported, the CDC issued its first agent summary statement for work with HTLV-III/LAV in 1986 (41). The statement included a summary of laboratory-associated infections with HTLV-III (HIV), the hazards that might be encountered in the laboratory, and advice on the safety precautions that should be taken by laboratories. Biosafety level (BSL) 2 precautions were recommended for work with clinical specimens, body fluids, or tissues from humans or laboratory animals *known or suspected to contain* HTLV-III/LAV (HIV). BSL 3 additional practices and containment equipment were recommended for activities involved with culturing research laboratory-scale amounts of the virus. A BSL 3 facility and BSL 3 practices and procedures were recommended for all work involving industrial-scale, large-volume concentrations of the virus (Table 5).

Reports issued by the CDC (43) in May 1987 documented that laboratory workers and other clinical staff were occupationally infected with HIV via nonintact skin and mucous membrane exposures. Because the HIV serostatus of the patient sources was unknown at the time of exposure and the exposures were nonparenteral, the CDC issued the "universal blood and body fluid precautions" recommendations in August 1987 (42). The main premise involves the *careful* handling of all blood and body fluids as if *all* were contaminated with HIV, HBV, or other blood-borne pathogens. This "universal precautions" concept formed the basis for all subsequent recommendations from the CDC (48, 51) and other professional organizations such as the National Committee for Clinical Laboratory Standards (NCCLS) (196). A summary of the universal precautions recommendations for clinical laboratories appears in Table 6.

The counterpart of universal precautions in a laboratory situation involves the *consistent* use of BSL 2 facilities and practices as outlined in the CDC/NIH manual *Biosafety in Microbiological and Biomedical Laboratories* (225–227; Appendix I). The BSL 2 precautions are most appropriate for clinical settings or when exposure to human blood, primary human tissue, or cell cultures is anticipated. Standard microbiological practices form the basis for BSL 2, with additional protection available from personal protective equipment (PPE) and BSCs when appropriate.

In 1988, two reports of research laboratory workers with documented occupational HIV infection prompted an investigation by an expert team to review possible sources of exposure and any need to revise current practices to reduce hazards in the research laboratory (46). Subsequently, an agent summary update was issued and included in the 1988 edition of *Biosafety in Microbiological and Biomedical Laboratories* (226). The expert team did not advise alteration of the CDC/NIH biosafety recommendations for laboratories but stressed the need for reinforcement of safety practices through proficiency and administrative discipline.

In addition to the advisory nature of the CDC/NIH guidelines, OSHA issued a final standard to regulate occupational exposure to blood-borne pathogens (262) (see Appendix II). The standard builds on the implementation of "universal precautions," specifying the need for control methods, training, compliance, and record keeping. The components of the OSHA standard are outlined in Table 7.

OSHA also recognizes that employees in HIV/HBV research laboratories and production facilities may be placed at a higher risk of infection after an exposure because of the concentrated preparations of viruses. Requirements for practices and special

TABLE 5 CDC/NIH recommended precautions for laboratory work with HIV-1[a]

Facility	Practices and procedures	Activities involving:
BSL 2	BSL 2	Clinical specimens Body fluids Human or animal tissues infected with HIV
BSL 2	BSL 3	Growing HIV at research laboratory scale Growing HIV-producing cell lines Working with concentrated HIV preparations Droplet or aerosol production
BSL 3	BSL 3	HIV at industrial-scale levels Large volume or high concentration Production and manipulation

[a]Adapted from reference 197.

TABLE 6 Summary of universal precautions for laboratories—CDC[a]

1. Universal precautions should apply to blood and all body fluids containing visible blood, semen, vaginal secretions, tissues, cerebrospinal fluid, synovial fluid, pleural fluid, peritoneal fluid, pericardial fluid, and amniotic fluid.
2. Hands should be washed immediately when contaminated with blood or other bodily fluids, after removing gloves, and after completing laboratory activities.
3. Use of needles and syringes should be limited to situations in which there is no alternative. If used, needles should not be recapped, purposely bent or broken by hand, removed from disposable syringes, or otherwise manipulated by hand. After use, disposable syringes and needles, scalpel blades, or other sharp items should be placed in puncture-resistant containers for disposal; these containers should be located as close as practical to the use area. Reusable sharps should be placed in a puncture-resistant container for safe transport to the processing area.
4. Laboratory workers should use protective barriers appropriate for the laboratory procedure and the type and extent of exposure anticipated. For example:
   All persons processing blood specimens should wear gloves.
   Phlebotomists should wear gloves when they have cuts, scratches, or other breaks in the skin, when hand contamination is predictable (i.e., uncooperative patient, or heel or finger sticks on infants and children), and when receiving training in phlebotomy.
   Surgical or examination gloves should not be washed or disinfected for reuse.
   General-purpose utility gloves should be used for housekeeping, instrument cleaning, and decontamination procedures and can be decontaminated and reused as long as they remain intact.
   Masks and protective eyewear or face shields should be worn if mucous membrane contact with blood or bodily fluids is anticipated (i.e., removing tops from vacuum tubes).
   Gowns, laboratory coats, or aprons should be worn during procedures that are likely to generate splashes of blood or bodily fluids and should be removed before leaving the laboratory.
   Routine procedures, such as histologic and pathologic studies or microbiologic culturing, do not require a BSC. BSCs (class I or II) should be used whenever procedures are conducted that have a high potential for generating droplets (i.e., blending, sonicating, and vigorous mixing).
5. All specimens of blood should be put in a well-constructed container with a secure lid to prevent leakage during transport.
6. Mechanical pipetting devices should be used in the laboratory. Mouth-pipetting must not be performed.
7. Laboratory work surfaces should be cleaned of visible material and then decontaminated with an appropriate chemical germicide after a blood or bodily fluid spill and when work activities are completed.
8. Contaminated materials used in laboratory tests should be decontaminated before reprocessing or be placed in bags and disposed of in accordance with institutional and regulatory policies for disposal of infective waste.
9. Contaminated scientific equipment should be clean and then decontaminated before repair in the laboratory or transport to the manufacturer.
10. Area posting of warning signs should be considered to remind employees of continuing hazards of infectious disease transmission in the laboratory.

[a]Modified from references 42, 48, and 51.

procedures, facility design, and additional training for these workplace situations are included in the OSHA standard and are consistent with the CDC/NIH laboratory biosafety guidelines for BSL 2 and 3.

Specific Precautions

OSHA has issued the blood-borne pathogen standard as a "performance" standard. That is, the employer has a mandate to develop an exposure control plan to provide a safe work environment but is allowed some flexibility in accomplishing this goal. The OSHA standard includes the basic philosophy of the CDC "universal precautions," along with combinations of engineering controls, work practices, and PPE to accomplish the intent of the standard (Appendix II). Exposure control plans for laboratories must adhere to the rules of the OSHA standard but can also benefit from safety recommendations from other professional organizations such as the CDC, NIH, or NCCLS. The following recommendations may be used to augment a laboratory safety plan .

Sharps Precautions

Because injuries from contaminated sharps represent the highest risk for HIV transmission, clinical and research laboratory safety plans should restrict the use of needles and other sharp instruments in the laboratory for use only when there is no alternative, such as performing phlebotomy. For many laboratory procedures, blunt cannulas or small-bore tubing can be substituted. If needles must be used,

TABLE 7 Summary of OSHA blood-borne pathogen standard requirements[a]

I. Exposure control plan (ECP): the establishment's written or oral policy for implementation of procedures relating to control of infectious disease hazards

II. Components of the ECP include:
- A. Exposure risk determination for all employees
- B. Control methods:
  1. Universal precautions: a method of infection control in which all human-derived blood and potentially infectious materials are treated as if known to be infectious for HIV or HBV
  2. Engineering controls: use of available technology and devices to isolate or remove hazards from the worker (biosafety cabinets [BSCs], puncture-resistant sharps containers, mechanical pipetting devices, and covered centrifuge canisters)
  3. Work practice controls: alterations in the manner in which a task is performed to reduce the likelihood of exposure to the worker (standard microbiologic practices in laboratories [e.g., Biosafety Level 1 practices], disposal of needles without recapping or breaking)
  4. Personal protective equipment (PPE): specialized clothing or equipment used by workers to protect themselves from exposures (gloves, gowns, laboratory coats, fluid-resistant aprons, face shields, masks, eye protection, and head and foot coverings)
  5. Additional requirements for HIV and HBV research laboratories and production facilities:
     Biosafety level 3 (BSL 3) special practices and containment equipment
     Research facility meets BSL 2 design criteria
     Production facility meets BSL 3 design criteria
- C. Housekeeping practices
- D. Laundry practices
- E. Regulated waste disposal
- F. Tags, labels, and bags
- G. Training and education programs: additional training for employees in HIV or HBV research laboratories and production facilities *before* work with HIV or HBV
- H. Hepatitis B vaccination
- I. Postexposure evaluation and follow-up
- J. Record keeping: includes medical records, training records, and maintaining availability of records

III. Administrative controls: to develop the ECP; to provide support of the ECP and provide accessibility of control methods, monitor compliance, and survey for effectiveness; and to investigate exposures for prevention of future occurrences

[a]From reference 262.

the use of "self-sheathing" needles designed to prevent needlesticks should be considered. Used needles should never be bent, broken, recapped, removed from disposable syringes, or otherwise manipulated by hand before disposal; rather, they should be carefully placed in conveniently located puncture-resistant containers (227). Removal of needles from nondisposable Vacutainer sleeves or syringes should be accomplished with a mechanical device such as forceps or hemostats or by using notched slots designed into needle boxes for safe removal of the needle. The OSHA standard allows a "one-handed" recapping technique only if there is no alternative feasible. All disposable sharps encountered in the laboratory, including pipettes, microtome blades, micropipette tips, capillary tubes, and slides, should also be carefully placed in conveniently located puncture-resistant containers for disposal. Nondisposable sharps should be placed in a hard-walled container for transport to a processing area.

Plasticware should be substituted for glassware whenever possible. Broken glassware should never be handled directly by hand but must be removed by mechanical means such as a brush and dustpan, tongs, or forceps. Cotton swabs can be used to retrieve small slivers of glass.

Engineering Controls

Recognizing that human behavior is inherently less reliable than mechanical controls, OSHA advocates the use of available technology and devices to isolate or remove hazards from the worker. The use of self-sheathing needles is an example of an engineer-

ing control to help isolate the worker from the hazard of needlestick exposure.

Another engineering control in the laboratory is the use of a properly maintained BSC to enclose work with a high potential for creating aerosols or droplets (i.e., blending, sonication, necropsy of infected animals, intranasal inoculation of animals, or opening lyophilized vials under pressure). *All* work with infectious material in an HIV research laboratory should be performed in a BSC or other physical containment device. For example, high-energy activities such as centrifugation that are performed outside a BSC should be designed for aerosol containment. Sealed safety cups or rotors should be used for centrifugation and changed out in a BSC. Before centrifugation tubes should be examined for cracks, and any glass fragments in the centrifuge cups should be carefully removed with forceps or hemostats. Microwell plate lids can be sealed with tape or replaced with adhesive-backed mylar film before centrifugation.

Plastic shielding can be used to reduce the exposure to splatter or droplets from fluorescent activated cell sorters or other automated laboratory equipment that might generate droplets of infectious material. Likewise, the Plexiglas radiation shield used in RT assays offers protection from splatter. However, if used in a BSC, the sloped top may divert airflow in the cabinet and must be removed to provide optimal protection by the BSC.

High-speed blenders and grinders are available that contain aerosols of infectious material but need to be opened in a BSC after processing. Enclosed electrical incinerators are preferable to open Bunsen burner flames for decontaminating bacteriologic loops to prevent splatter and may be used within or outside of a BSC.

Work Practice Controls

The manner in which a task is performed can minimize the likelihood of exposures in the laboratory. For example, careful disposal of used needles without recapping or otherwise manipulating by hand can reduce the likelihood of needlesticks.

Standard microbiological practices have been recommended by CDC and NIH guidelines (226, 227) for all laboratory containment levels (see Appendix I). Most of the practices are designed to prevent indirect transmission of infectious material from environmental surfaces to the hands and from hands to the mouth or mucous membranes. Such practices include prohibition of mouth pipetting, eating, drinking, smoking, applying cosmetics, or handling contact lenses in the laboratory and attention to environmental decontamination.

One of the best work practices for any laboratory setting is that of frequent and adequate handwashing when hands are visibly contaminated, after completion of work, before leaving the laboratory, after removing gloves, and before eating, drinking, smoking, or changing contact lenses. Any standard handwashing product is adequate, but products should be avoided that disrupt skin integrity. When knee- or foot pedal-controlled faucets are not available, faucets should be turned off by using the same paper towels used to dry hands to prevent recontamination of hands. Proper attention to handwashing will prevent inadvertent transfer of infectious material from hands to mucous membranes (see also Chapter 17).

In most clinical settings, skin lesions may be covered by occlusive dressings and, if lesions are on the hands, gloves worn over the dressings to prevent contamination of nonintact skin. However, workers with skin lesions or dermatitis on hands or wrists should not perform procedures with concentrated HIV material even if wearing gloves. Other work practices can reduce the amount of splatter from laboratory procedures. Covering pressurized vials with plastic-backed or alcohol-soaked gauze when removing needles or when removing tops of pressurized Vacutainer tubes will minimize the exposure to splatter. To prevent popping stoppers on evacuated tubes or vials, blood should never be forced into the tube by exerting pressure on the syringe plunger; rather, tubes and vials should be filled by internal vacuum only. Extreme caution should be used when handling pressurized systems such as continuous-flow centrifuges, apheresis, or dialysis equipment. Use of imperviously backed absorbent material ("lab diapers") can reduce the amount of splatter on laboratory work surfaces when liquids accidentally leak or fall during laboratory procedures and can aid in laboratory cleanup. The air intake and exhaust grills in BSCs must be kept clear of any surface covers or equipment.

Safe transport of specimens or infectious material within the laboratory or to other areas can minimize the potential for accidental spills or injuries. Specimens should be placed in a closed leakproof primary container and covered with a secondary container (i.e., a plastic bag of appropriate size and strength) to contain any leaks during transport. The OSHA regulations do not mandate labeling or color-coding specimens if the specimens are handled only within the facility, a policy implementing "universal precautions" is in effect, and the containers are recognizable as human specimens. Bulk samples may be safely transported in a rack within a sealable plastic container such as a modified "tackle box." The box should be labeled with a biohazard symbol

or be color-coded if the contents are not clearly visible as specimens.

Luer caps should be used to transport syringes (after needles are removed with forceps or hemostats and properly disposed) or needles carefully recapped using a one-handed technique. Capillary tubes should be transported in a solid-walled secondary container such as a screw-top test tube. Transport of cultures or hemocytometers from the BSC within the laboratory may be facilitated by placing them on a tray to limit the number of trips and opportunities for spillage.

Designation of "clean" versus "dirty" areas of the laboratory or within BSCs can help prevent inadvertent contamination. Work should be planned to move from clean areas to dirty areas. Routine cleaning of work surfaces must be performed after procedures are completed and at the end of each work shift, with additional decontamination as needed for spills. Routine cleaning can be accomplished using a variety of disinfectants including iodophors registered as hard-surface disinfectants, phenolics, and 70% ethanol (with consideration given to the need for longer contact time when decontaminating dried viral cultures [116]). Diluted bleach has been most widely used for routine disinfection (10% bleach [0.5% sodium hypochlorite] for porous surfaces and 1% bleach [0.05% sodium hypochlorite] for cleaned, hard, and smooth surfaces). Aldehydes are not recommended for surfaces because of their potential toxicity. Further information on disinfection may be found in Chapter 17.

Prompt decontamination is important after spills of infectious materials, because HIV is able to survive for several hours in the environment (Table 1). Appropriate spill clean-up in a clinical setting should be carried out by a trained employee using appropriate PPE and the following methods:

1. Absorb the spill with towels or "lab diapers" to remove the extraneous organic material.
2. Clean with soap and water.
3. Decontaminate with an appropriate disinfectant. (The CDC recommends an EPA-registered "hospital disinfectant" that is also "tuberculocidal"; or a 1 to 10% bleach solution [one part of household bleach to nine parts of water] is sufficient [42].)

Large spills of cultured or concentrated agents may be safely handled with an extra step:

1. Flood the spill with an appropriate disinfectant *or* absorb the spill with granular material impregnated with disinfectant.
2. Carefully soak up the liquid material with absorbent material (paper towels) or wipe or scrape up the granular absorbent material and dispose of according to the waste disposal policy.
3. Clean the area with soap and water.
4. Decontaminate with fresh disinfectant.

Laboratory equipment (analyzers, centrifuges, pipettors) should be checked routinely for contamination and appropriately decontaminated after use with potentially infectious materials. Equipment sent for repair must be decontaminated before leaving the laboratory or labeled as to the biohazard involved and packaged to prevent the exposure of transport and repair personnel.

Because the intent of the OSHA blood-borne pathogen standard is worker protection, the rules for appropriate waste disposal emphasize adequate packaging. Sharps disposal containers must be puncture- and leakproof as well as easily accessible. Other regulated ("infectious" or "medical") waste must be placed in leakproof containers or bags that are color-coded red or orange or labeled with the word *biohazard* or the universal biohazard symbol. All disposal containers should be replaced before they are full.

Blood or body fluids may be disposed of by carefully pouring down the sanitary sewer if local health codes permit but preferably not poured into a sink used mainly for handwashing. Liquid and solid culture materials, however, *must* be decontaminated before disposal, most commonly by steam sterilization (autoclaving). Tissues, body parts, and infected animal carcasses are generally incinerated. *All* contaminated laboratory waste from HIV research-scale laboratories or production facilities and animal rooms must be decontaminated before disposal (BSL 3 practices). Additional regulated waste definitions and requirements may exist locally and must be consulted for proper disposal policies.

Personal Protective Equipment

Another strategy to minimize worker exposure to infectious material is the use of PPEs that are appropriate for the laboratory procedure and the type and extent of exposure anticipated. Examples include a variety of gloves, gowns, aprons, and face, shoe, and head protection. Appropriate selection and use of PPEs are discussed in more detail in Chapters 11 and 13. PPE may be used in combination with engineering controls or work practices for maximum worker protection.

Gloves are required by OSHA when hand contact with blood, other potentially infectious materials, mucous membranes, or nonintact skin is reasonably anticipated. The federal regulations also require gloves when handling or touching contaminated

items or surfaces and for performing vascular access procedures. (The exception for trained phlebotomists [Table 6] is only allowed in volunteer blood donation centers.) Gloves are appropriate in the laboratory when handling clinical specimens, infected animals, or soiled equipment, when performing all laboratory procedures with potentially infectious materials in clinical or research laboratories, when cleaning spills, and when handling waste.

For routine procedures, vinyl or latex gloves are effective when appropriately used for prevention of skin exposure to infectious materials. These gloves are not sufficient protection against puncture wounds from needles or sharps. However, there is evidence of a "wiping" function that may reduce the amount of blood or infectious material brought through from the outside of the needle as it penetrates a glove or combination of gloves. Johnson et al. (138) found that two or three layers of latex gloves appeared to reduce the frequency of HIV-1 transfer by surgical needles to cell cultures. They also found that Kevlar gloves (untreated), Kevlar gloves (treated with the virucidal compound nonoxynol-9), and nonoxynol-9-treated cotton gloves used as intermediate layers between two layers of latex gloves significantly reduced the amount of HIV-1 transfer when compared with a single latex glove barrier. Gerberding et al. (103) reported that when surgeons wear double gloves, the rate of puncture of the inner glove is three times less than the rate of puncture of a single glove.

Other gloves are available that provide puncture "resistance" such as stainless steel mesh (chain mail) gloves to protect against injury from large sharp edges such as knife blades. Nitrile gloves (synthetic rubber) have some degree of puncture resistance that may eliminate problems of tears from rings or fingernails, yet retain the necessary dexterity required for performing laboratory procedures. A thin leather glove has been developed that can be worn under latex gloves for an additional barrier against needlesticks or animal bites. Even heavyweight utility gloves (dishwashing gloves) provide extra protection and should be worn when the procedure permits, such as cleaning contaminated equipment or spills.

Undetected holes and leaks require that gloves be inspected by the user and changed when necessary. The Food and Drug Administration has issued acceptable quality limits for defects at 2.5% defective for surgeons' gloves and 4.0% for latex examination gloves (263), although the acceptable quality limit varies widely among manufacturers. The reported percentage of defects caused by holes for nonsterile latex gloves ranges from 0 to 32%, and for nonsterile vinyl gloves, from 0 to 42% (196). Clearly, for high-risk situations such as gross contamination of gloves with blood, bloody body fluid, or high concentrations of HIV-1, the use of double gloves will lower the risk of hand contamination from seepage through undetected glove defects. Although they are more puncture-resistant, nitrile gloves are designed to tear apart when any pressure is applied to a hole in the glove, so that any defect in the glove can be detected.

Disposable latex and vinyl gloves must not be washed or disinfected for reuse. Detergents may cause enhanced penetration of liquids through undetected holes, causing a "wicking" effect (48, 196). Disinfectants, such as 70% ethanol, can also enhance the penetration of the glove barrier and facilitate deterioration (152, 196).

Gloves must be changed when visibly contaminated, torn, or defective or when tasks are completed. Because hands may be inadvertently contaminated from laboratory surfaces, gloves should be removed before handling telephones, doorknobs, or "clean" equipment. Alternatively, "dirty" equipment may be designated and marked to be handled only with gloved hands. Laboratory workers should practice the aseptic technique for glove removal (i.e., the contaminated outside of the gloves is turned inside as gloves are removed to protect the worker from skin contamination). Hands should always be washed after glove removal.

When soiling of clothing is anticipated, laboratory coats, gowns, or aprons are recommended. However, when a potential for splashing or spraying exists, solid-front, appropriately fluid-resistant gowns should be selected. If the anticipated exposure involves soaking, solid-front fluidproof gowns are required, as well as hoods or caps, facial protection, and shoe covers. BSL 3 practices advise a solid-front or wrap-around, long-sleeved gown or coveralls for adequate protection in research laboratories or production facilities.

Gowns with tightly fitting wrists or elasticized sleeves should be worn for work in BSCs. Alternatively, water-resistant "gauntlets" that provide a barrier between the glove and the laboratory coat are available to reduce skin exposure of the wrist and arm.

Laboratory coats or gowns should not be worn outside the laboratory. In HIV-1 research laboratories or production facilities, the gowns or other protective clothing must be decontaminated before laundering or disposal (BSL 3 practices).

When splashing of blood or infectious material into the mucous membranes of the face is anticipated, a mask and goggles or face shield must be

used. Most laboratory procedures involving this degree of potential exposure should be conducted within containment equipment such as a BSC. Face protection might be needed for activities conducted outside a BSC, such as performing an arterial puncture, removing cryogenic samples from liquid nitrogen, or in some animal care areas. Masks and eye goggles or face shields also serve a passive function as a means of preventing accidental contact of contaminated gloved hands with the eyes, nose, and mouth during the course of work activities.

Whatever the PPE needs of any particular laboratory, OSHA requires that the employer provide an adequate supply of PPEs in the appropriate sizes. Hypoallergenic gloves must be available for employees who develop allergies to glove material or the powder inside gloves. Any defective PPE must be replaced, and reusable protective clothing must be laundered and maintained by the institution. Finally, all laboratory workers must be instructed in the proper use of PPEs and their location.

Animal Research

Nonhuman Primates

Until recently, HIV studies in animals were restricted to nonhuman primates. Chimpanzees can be successfully infected with HIV-1, although they do not demonstrate disease (91). A potentially new animal model of HIV infection has been reported by Agy et al. (2). This group has successfully infected *Macaca nemestrina* with HIV-1. Like chimpanzees, this animal demonstrates infection but not disease. The advantages are the lower cost and greater availability of the animals.

Simian immunodeficiency virus (SIV), a retrovirus closely related to HIV-1 and HIV-2, has been isolated from several species of nonhuman primates (African green monkeys [200], sooty mangabeys [94], and macaques [71]) and is used as a model for HIV infection. Two laboratory workers have sustained exposures (one needlestick, one open skin lesion) and subsequently seroconverted with antibodies to SIV (59). Both remain well, with no clinical or laboratory evidence of immunodeficiency to date. These two laboratory-acquired infections emphasize the need to adhere to the specific guidelines that have been published for research with nonhuman primates to minimize the risk of HIV-1 and SIV transmission to laboratory workers and animal handlers (23, 45, 50). BSL 2 practices, containment equipment, and facilities for animals (see Appendix I) are recommended in both instances, with an additional note to use face shields or surgical masks and eye shields as appropriate in animal rooms to protect the mucous membranes of the eyes, nose, and mouth from excreta that may be thrown by animals. To avoid accidental injuries during inoculations or other procedures on animals, both chemical and physical restraints may be used (270).

SCID Mice

Two mouse models were developed in 1988 that allow in vivo studies of HIV in human cells. The models were constructed by engrafting either human peripheral blood leukocytes (192) or human thymus, lymph node, and liver tissue (SCID-hu) (183) into severe combined immunodeficient (SCID) mice. The human peripheral blood leukocyte SCID mice and SCID-hu mice can then be infected with HIV-1 and demonstrate syndromes that closely resemble human infection (195).

To minimize the potential risk to laboratory workers and the community from research with HIV-infected mice, all studies were initially conducted in containment facilities following practices that met or exceeded BSL 3 standards. In 1990, a working group sponsored by the National Institute of Allergy and Infectious Diseases reviewed studies conducted on the C.B17-*scid/scid* mouse (189). The participants concluded that the level of viremia in these infected mice does not exceed that of humans, and the likelihood of HIV interaction with endogenous viruses to produce a pseudotype virus with an altered route of transmission is low. It was agreed that research on the HIV-infected SCID mouse could be conducted safely in BSL 2 facilities using BSL 3 practices. However, BSL 2 facilities should incorporate design features that prevent escape of HIV-infected animals. The workshop participants also agreed that animal studies likely to generate HIV pseudotypes should be conducted under BSL 3 conditions until further evaluation of this potential. Also, any research in which HIV is purposely coinfected with mouse amphotropic or xenotropic retroviruses (e.g., murine leukemia virus) or human lymphocytotrophic viruses (e.g., Epstein-Barr virus or cytomegalovirus) should be conducted at BSL 3. Appropriate precautions should also be taken for work with SCID mice other than type C.B17. Information on the risk of exposure to replication-competent retroviruses can be found in Chapter 9.

Transgenic Mice

Transgenic mice have been developed as another animal model that contain inserted copies of HIV proviral DNA. Leonard et al. (163) demonstrated that some transgenic mice develop a fatal disease that mimics AIDS in humans. Although no biosafety recommendations have been published specifically

addressing this animal model, concerns over animals escaping, mating in the wild, and possibly extending the host range of the virus have prompted researchers to use BSL 3 facilities primarily for animal containment (270).

Other

Another small animal model, the New Zealand white rabbit, is used for HIV in vivo research (155), constructed by injection of an HIV-infected human T-cell line. Infected rabbits have also been studied in BSL 2 facilities with manipulations carried out using BSL 3 practices by the laboratory workers.

Other Research Concerns

Vaccinia Vectors

Advances in recombinant DNA research techniques and peptide synthesis have enabled researchers to identify and clone proviral DNA forms of HIV, with expression of viral proteins. The viral proteins can then be used for drug and vaccine development studies (240). The vaccinia virus has been genetically engineered to contain foreign DNA from one or more infectious agents, including HIV. The recombinant vaccinia virus can then express the protein antigens of HIV (62, 193). Because laboratory-acquired infections with vaccinia and recombinant vaccinia have been reported (141, 206), the CDC recommends that the vaccinia vaccine be given to laboratory workers who directly handle vaccinia cultures or who handle animals contaminated or infected with vaccinia or recombinant vaccinia (58).

HIV Proteins

Because some of the expressed proteins may be immunogenic, concern has been expressed that laboratory workers exposed to the *proteins* may develop HIV-specific antibodies and demonstrate a false-positive Western blot test for determination of HIV infection (221). Although the initial concern is a psychosocial one, the impact on the workers' immune response to any subsequent HIV vaccination attempt is unknown.

HIV Proviral DNA

Letvin et al. (164) infected macaques by inoculation with SIV proviral DNA. They speculate that HIV viral DNA may be infectious for laboratory workers and call for researchers to evaluate DNA handling techniques carefully.

The fast pace of HIV research developments and techniques requires careful planning to prevent exposures to HIV, HIV proteins, or HIV proviral DNA. Attention to the BSL 2 or 3 recommendations, as well as training and monitoring laboratory workers for safe work practices, will minimize this risk.

Employee Training and Monitoring

One of the most important components of an exposure control plan for the laboratory is a formal training program. Mere "on-the-job" training is not acceptable as adequate safety training in the laboratory. Recommendations from the CDC (46) and the NCCLS (196) that emphasize education of laboratory workers have been incorporated into the OSHA blood-borne pathogen standard (262; Appendix II).

Interactive training sessions must be conducted on initial hire and with annual updates by a person knowledgeable about the standard. Employees must be educated regarding their risks and the institution's plan to control these risks. Specific required components of the training program may be found in Appendix II.

Recognizing the increased risk of working with concentrated viral preparations, OSHA requires that employees in HIV research laboratories and production facilities receive *additional* initial training. Employees in these situations must demonstrate proficiency in standard microbiological practices as well as practices and techniques specific to the facility before work with HIV. This might include prior experience in handling human pathogens or tissue cultures or participation in a training program with a progression of work activities to develop proficiency before pathogens are handled.

Employers must ensure compliance with the OSHA standard. The CDC (46) and the NCCLS (196) recommend that workplace practices be monitored at regular intervals by a biosafety expert. The NCCLS suggests that audits be conducted to evaluate the existence and effectiveness of training programs and the appropriate training of the safety instructors. The audit should also examine the adequacy of the laboratory facilities and equipment, the standard operating practices, and the written safety protocols. Corrective measures should be implemented if needed. If breaches in protocol are detected, employees should be re-educated and, if necessary, disciplinary action taken.

OCCUPATIONAL HEALTH ISSUES

Vaccination

Historically, vaccines have been the most effective and safest prevention strategy in a biosafety program. One of the best examples of this approach for the laboratory is the hepatitis B vaccine, now man-

dated by OSHA as an important component of a workplace exposure control program (262). However, the unique properties of the HIV virus and the complex social issues involved with the disease have made efforts to design and test a safe effective vaccine very difficult. Obstacles to the development of a vaccine include the many antigenic variants of the virus, the fact that HIV is not only transmitted as free virus but integrated into the DNA of the host cells, the risk of immunopathology by viral proteins, no known animal model that consistently demonstrates infection and disease, the need for systemic *and* mucosal immunity, the unknown long-term protective response of antibodies, and the complex issues associated with strategies for large-scale testing of a candidate vaccine (19, 66).

Vaccine Strategies

The most common approach to HIV vaccine development to date is the use of protein subunits of the virus, via recombinant DNA and genetic engineering (231), purified native proteins from infected cells (11), or synthetic peptides from the HIV envelope or core (149). Seven clinical trials are in progress using HIV-1 recombinant envelope vaccines and two trials using core peptides (98). Multiple antigens may be required, however, for effective protection. Soluble subunit vaccines rarely induce cytotoxic responses unless presented in a special adjuvant or delivery system.

Such an approach is that of live virus recombinants (non-HIV viruses such as vaccinia) used as vectors combined with HIV envelope genes (62, 193) with a follow-up booster with recombinant envelope protein (186). The "prime-boost" combination produces a strong cellular immune response. However, large efficacy trials using vaccinia as a vector will not be entirely safe unless the vaccinia virus is further attenuated (98). Other attenuated live vectors in development include recombinant adenovirus (64), poliovirus (82), *Salmonella* (1), and Calmette-Guerin bacillus (253). Again, safety for immunocompromised recipients is a concern when inoculating with live vectors. Other vaccine strategies proposed have been the use of a killed HIV-1 virus (178), a nonpathogenic, genetically altered HIV variant (75, 87), or an anti-idiotype vaccine to mimic CD4 receptors to "neutralize" the virus (70).

Problems with the experimental vaccines to date include the requirement for multiple injections over several months, the short duration of immunity provided by the vaccine, and the lack of protection when animals are challenged by IV or genital infection with high doses of virus (98). Also, immunity has not been demonstrated against the wide variety of HIV strains found in nature, nor has the necessary induction of $CD8^+$ cytotoxic lymphocyte activity been demonstrated.

Postinfection Vaccination

Although vaccines to prevent infection may not be currently attainable, vaccines are being developed that may prevent or delay the onset of the disease AIDS (233). This "postinfection" or "therapeutic" strategy relies on the immunization of asymptomatic HIV-infected individuals to boost their protective response, reduce the viral burden, and prevent the clinical progression to AIDS. Therapeutic trials with HIV gp160 vaccine and killed HIV (the Salk vaccine) are under way in humans.

Despite the failure to date to develop an effective, practical vaccine for humans, the commitment of the federal government, private industry, and academia is encouraging for the future. There is no doubt that when such a vaccine is approved, OSHA will require its widespread use in the health care and laboratory settings as an integral component of an exposure control program.

Postexposure Evaluation Program

The implementation of a laboratory exposure control program that includes universal precautions and the recommendations from the CDC and the NIH may reduce the incidence of occupational exposure to HIV; however, use of prevention strategies will not entirely eliminate the risk of accidental exposures to HIV and subsequent occupational infection. OSHA estimates that full compliance with the blood-borne pathogen standard would reduce the risk of mucous membrane and skin exposure by 90% and the risk of parenteral exposure by 50% (261). Therefore, a postexposure evaluation program is a necessary and mandated component of a laboratory safety program.

Laboratories handling blood, other potentially infectious materials, or concentrated HIV viral material must adhere to the OSHA postexposure protocol that requires confidential medical evaluation, follow-up, and documentation of an exposure incident. OSHA defines an "exposure incident" as a "specific eye, mouth, other mucous membrane, non-intact skin, or parenteral contact with blood or other potentially infectious materials that results from the performance of an employee's duties" (262). The NCCLS and the CDC have also published guidelines for HIV-exposure evaluation that can serve to augment and complement the OSHA standard (42, 43, 196). The recommendations from these three organizations are summarized in Table 8.

TABLE 8 Postexposure evaluation and management for HIV-1[a]

	OSHA	NCCLS	CDC
Source	Document route and circumstances of exposure Identify source and test after consent within legal restrictions and as soon as possible	Test source with consent or source material in an anonymous manner	Document route and circumstances of exposure Test source with consent
Exposed worker (general)	Counsel employee about: Source serostatus Applicable laws Further needed evaluations Employee's blood collected and tested after consent		
Source is HIV(+) or refuses test	Not addressed	Counsel employee about: Risk of infection Reporting any acute illness Implications of HIV testing AZT prophylaxis Following CDC recommendations for prevention of HIV transmission during the first 6–12 weeks after exposure	Counsel employee about: Risk of infection Reporting any acute illness Following CDC recommendations for prevention of HIV transmission during first 6–12 weeks after exposure
		Test exposed employee after consent within 48 h	Medical evaluation of exposed employee
		Medical evaluation of exposed employee	
Follow-up	Evaluate any illness	Evaluate any illness	Test exposed employee after consent as soon as possible Evaluate any illness
Treatment	As recommended by Public Health Service	If baseline negative, test employee for HIV infection at 6 and 12 weeks and 6, 9, 12, and 24 months after exposure If worker requests and is counseled, AZT should be given, case should be reported to CDC, and follow-up period should be extended	If baseline negative, test employee for HIV infection at 6 and 12 weeks and 6 months after exposure (minimum) No recommendations for or against the use of AZT prophylaxis If AZT given, counseling and informed consent of employee obtained
Source is HIV(–)	Not addressed	Test exposed employee with consent at 3 and 6 months	Optional baseline test of exposed employee and at 12 weeks postexposure (particularly if source is in high-risk group)
Other	Employee receives a health care professional's written opinion of evaluation Medical records maintained for term of employment plus 30 years	Serologic testing available for employees who think they may have been occupationally exposed	Serologic testing available for employees who think they may have been occupationally exposed

[a]Modified from references 42, 43, 196, and 262.

All three organizations suggest that the exposure source material be evaluated for evidence of HIV-1 virus that might include HIV antibody testing or nontraditional tests such as HIV antigen or HIV DNA in peripheral blood mononuclear cells using the polymerase chain reaction. Because HIV antigens and viral DNA may be present in serum before antibodies are detectable, the nontraditional tests may be valuable when testing a source individual who tests HIV antibody negative but who is a member of a high-risk group for HIV infection. The NCCLS also suggests that seronegative sources who are members of high-risk groups be retested at 3 to 6 months if possible (196). The CDC recommends an optional baseline test of the exposed employee and a follow-up test at 12 weeks if the seronegative source is in a high-risk group (42).

The three organizations also require counseling of the exposed employees regarding the source serostatus, the associated risk of HIV-1 transmission, any applicable legal consequences, and the need for medical evaluation of any acute febrile illness the employee may experience postexposure. Such an illness, characterized by fever, rash, or lymphadenopathy, developing within 12 weeks of exposure has been reported in documented occupationally acquired HIV infections (175) and may indicate an acute HIV infection. During the first 6 to 12 weeks after the exposure, when infected employees may not have yet seroconverted, exposed workers should also be informed to follow public health service recommendations for preventing transmission of HIV (44). These recommendations include refraining from blood donations, abstaining from sex or use of safe sex measures, and no sharing of personal items such as razors or toothbrushes.

Although OSHA requires serologic testing of employees (with consent) after any occupational exposure incident, the CDC and the NCCLS recommend voluntary baseline testing only after exposures to an HIV-positive source or a source who refuses testing. The CDC and the NCCLS both recommend sequential serologic HIV testing of the exposed employee if the initial baseline serum is negative. The CDC recommends retesting periodically for a minimum of 6 months postexposure (e.g., 6 weeks, 12 weeks, and 6 months). Delayed seroconversion among health care workers has not been documented, so routine testing beyond 6 months is probably not indicated (102). The NCCLS, however, recommends additional testing at 9, 12, and 24 months because of the *possibility* of late seroconversion. The extension of postexposure serologic testing should also be considered if the employee has been given prophylactic AZT, because the drug has been shown to alter the course of HIV infection in animals (184), resulting in later detection of the virus than in animals not given AZT. Certainly, the employee should be tested if any signs or symptoms of HIV infection should occur after the routine testing period is over.

In addition to traditional HIV antibody testing, Henderson et al. (123) used antigen capture assays and polymerase chain reaction evaluations for employees with known exposure to HIV at the NIH. These tests failed to provide an earlier diagnosis of occupationally transmitted infection than could be detected by the traditional HIV antibody test. However, such nontraditional testing might be useful for evaluation of an exposed employee experiencing an acute illness before antibody conversion.

Both the CDC and the NCCLS recommend serologic testing be made available to employees who think they have been occupationally exposed to HIV-1. This might occur after an exposure to a source that cannot be identified or tested. No organization recommends routine serologic testing of clinical health care workers for HIV-1; however, the CDC/NIH Biosafety Guidelines call for "medical surveillance programs" in "all laboratories that test specimens, do research, or produce reagents involving HIV" (45).

The CDC and the NIH recommend that baseline serum samples for all HIV-1 research laboratory personnel be collected and stored, according to BSL 3 practices (45). Also, the expert team convened by the director of the NIH in 1988 to review safety practices in laboratories producing highly concentrated HIV recommended a medical surveillance serology program for these facilities (46). They recommended that serum samples be obtained at least once a year from the laboratory workers and analyzed for seroconversion. Results should be reported to individual workers in a timely and confidential manner, with counseling services available for any occupationally infected workers.

Postexposure Treatment

Azidothymidine

Because there is no approved effective vaccine for HIV-1, prophylactic use of AZT (azidothymidine or zidovudine) has been suggested and implemented in several medical centers in an attempt to prevent infection with the HIV virus (124). Fischl et al. (86) provided the first evidence of the efficacy of AZT in prolonging the life of HIV-1-infected patients. The basis for the efficacy of AZT is its inhibition of the viral RT activity that is necessary for viral replication. If AZT is to be used prophylactically, it is essen-

tial that it be given as soon as possible after exposure.

Attempts have been made to assess the efficacy of AZT prophylaxis after retroviral exposure in animals (184, 230, 241, 257) and humans (55) with mixed results. Animal studies have demonstrated prevention or alteration in the course of infection. AZT given between 1 and 4 h after inoculation of animal retroviruses seems to provide protection in mice and cats (230, 257). However, a study of macaque monkeys failed to demonstrate prevention of infection with SIV in two of three monkeys treated with AZT within 1 h of viral inoculation (181).

Recently, the SCID-hu mouse model has been used to evaluate AZT prophylactic activity on human hematolymphoid systems exposed to HIV (184, 241). McCune et al. (184) demonstrated that, even when AZT coverage is started 24 h before inoculation of HIV, some cells in the human thymus of SCID-hu mice show signs of infection at 2 weeks postinjection with HIV. The same research group (241) found that AZT suppressed HIV infection in a time-dependent manner (<2 h) after HIV inoculation of SCID-hu mice. The relevance of these animal studies to HIV infection is unknown.

Insufficient data exist to assess the efficacy of prophylactic AZT in humans after occupational exposure. Because of the small risk of occupational HIV transmission after exposure, it is estimated that a minimum of 3,000 enrollees in a double-blind, placebo-controlled trial would be needed to demonstrate significance of AZT prophylactic efficacy at a 5% level (121). Two attempts at such a study have been initiated. One study was sponsored by Burroughs-Wellcome in which a 6-week course of AZT (200 mg every 4 h) was administered to 49 clinically exposed health care workers (45 received placebo) (55). None was infected in either group. Because of the difficulty encountered in subject accrual, the study was discontinued in 1989 with no conclusive information. Likewise, the National Institute of Allergy and Infectious Diseases sponsored an open study for AZT prophylaxis after massive exposure to HIV-infected material (55) such as HIV-contaminated blood transfusion or exposure to high concentrations of HIV. Of three persons enrolled in this study and reported, two remained seronegative 3 and 11 months after exposure and AZT prophylaxis. This study was also discontinued in February 1991 with no conclusive information.

In 1991, investigators at the Clinical Center of the NIH and San Francisco General Hospital, with support from Burroughs-Wellcome, initiated a multicenter study of AZT toxicity that involves 14 hospitals. It is hoped that this large study will provide much-needed data regarding the toxicity and, perhaps, efficacy of prophylactic AZT (102).

The CDC has not made a recommendation for or against the use of AZT for prophylaxis because of the lack of relevant data. However, in 1988, the CDC expanded its ongoing prospective, voluntary surveillance of workers with occupational exposure to HIV to include information on postexposure chemoprophylaxis. Between October 1988 and June 1992, 444 workers reported percutaneous injuries and were followed for toxicity and efficacy of AZT prophylaxis. No seroconversions occurred in the workers who were not given AZT, but 1 seroconversion occurred among the 143 workers who were given AZT prophylactically, even though AZT was taken within 2 h after a needlestick (260).

Other reports of AZT prophylaxis failure have been reported in seven health care workers after percutaneous exposure to HIV-infected blood (5, 168, 169, 256, 260). Anecdotal reports of AZT failure have also been reported after blood transfusion from an HIV-infected donor (55), an accidental IV injection of 100 to 200 µl of HIV-contaminated blood (157), and self-inoculation of HIV-contaminated blood (78).

Decisions regarding AZT prophylaxis should be made on an individual basis in accordance with a defined institutional policy. Considerations for AZT administration should include

- The unknown efficacy of prophylactic AZT
- The possible side effects and toxicity
- The unknown teratogenicity and mutagenicity
- The unknown optimal dose and duration of dose
- The unknown "grace period" during which AZT should be given

Employees must be counseled regarding these issues and the diversity of opinions among physicians regarding this experimental use of AZT. Informed consent of the employee should be obtained and blood counts and chemistries monitored every 2 weeks. The CDC and the NCCLS also recommend an extended period of follow-up serologies if AZT is given, because the animal studies suggest an alteration in the infection process. AZT should be used only as an experimental option for informed employees when resources and expertise to monitor therapy are available (102).

Passive Immunotherapy

Another approach to postexposure treatment for prevention of HIV-1 infection is that of passive immunity with high concentrations of HIV-1 antibody, similar to the hepatitis B immunoglobulin strategy,

for immediate temporary protection. Prince et al. (213) found that anti-HIV-1 globulin extracted from HIV-infected persons failed to provide protection in chimpanzees when challenged with a large dose of HIV (400 $TCID_{50}$). A later study demonstrated that a single high dose of anti-HIV-1 globulin or high titers of soluble CD4-IgG given before inoculation of a smaller challenge of HIV-1 (120 $TCID_{50}$) protected chimpanzees from infection (266). Likewise, passive immunization with high antibody titers from immune macaques prevented infection of five of seven cynomolgous monkeys with HIV-2 and SIV (217). Further studies on postexposure prophylaxis are in progress and may provide additional strategies for prevention of HIV infection in infants born to HIV-infected mothers or in employees after occupational exposures.

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